

# Proceedings of the Scottish Thoracic Society and the Thoracic Society

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## **Anaerobic flora of the respiratory tract in non-infected patients**

B WATT, RF WILLEY, GK CROMPTON, IWB GRANT One approach to the laboratory diagnosis of anaerobic respiratory tract infections is to look for quantitative and qualitative differences between the anaerobic flora of the upper and lower respiratory tract. In this preliminary study, we undertook such a comparison in 50 patients with non-infective conditions of the respiratory tract. Samples were taken from the upper respiratory tract by expectoration and from the lower respiratory tract at diagnostic bronchoscopy or by tracheal aspiration. Samples were placed in transport media and sent promptly to the laboratory. Appropriate media were seeded and incubated anaerobically for up to seven days. Anaerobic isolates were separated and identified. The results were variable: in some patients without a tracheostomy, upper and lower respiratory tract flora was identical; in others the anaerobic flora of the upper respiratory tract was absent from the lower respiratory tract samples. In a proportion of patients with tracheostomies, the anaerobic flora of the saliva was similar to that found in the tracheal secretions. The significance of these findings is discussed in relation to problems of diagnosis of anaerobic respiratory tract infections.

## **Lymphangiomyomatosis and benign metastasising leiomyoma: a clinical spectrum responsive to oophorectomy**

WW ADDINGTON, AS BANNER, CB CARRINGTON, WB EMORY, CF KITTLE, G LEONARD Lymphangiomyomatosis and benign metastasising leiomyoma are thought to represent distinct clinical disorders with pulmonary manifestations characterised by smooth muscle proliferation. Both diseases occur exclusively in women and tend to follow a progressive course before the menopause. Lymphangiomyomatosis is characterised by interstitial disease of the lung with prominent pleural complications consisting of pneumothorax and chylothorax. Benign metastasising leiomyoma, on the other hand, presents with nodular disease, and pleural complications are unheard of. We present three cases with differing pathological characteristics, yet with overlapping clinical manifestations. All presented with interstitial disease of the lung, two with pneumothoraces and the third with a chylothorax. Two patients had restrictive disorders while the third had airways obstruction. All patients underwent oophorectomy. Two patients exhibited marked roentgenographic clearing

while the third appeared to stabilise. There was marked functional improvement in one patient while pulmonary function stabilised in the other two. All patients continue to do well with no further pleural complications and all are asymptomatic three, five, and 11 years after oophorectomy.

## **Six cases of primary lymphocytic lymphoma of lung: pathology and clinical management**

AMANDA HERBERT, DH WRIGHT, RC GODFREY, JL SMITH Six patients presented with persistent, localised shadows on chest x-ray. They were either asymptomatic or had symptoms of cough and weight loss. Localised lymphocytic tumours were resected, and none has recurred. During follow-up one patient developed coeliac disease and one died from a gastric lymphoma. It is difficult to decide whether these lesions are reactive or neoplastic. In the past "pseudolymphomas" and "true lymphomas" have been differentiated on morphological grounds, largely depending on the presence or absence of germinal centres (Saltztein. *Cancer* 1963;16:928). This does not correlate with behaviour since most of the "true lymphomas" remain localised. Neoplastic B-lymphocytes can be identified by their monoclonal immunoglobulin production. An immunoperoxidase technique for formalin fixed tissue only demonstrated monoclonal cytoplasmic immunoglobulin in case 5 where there was plasmacytic differentiation. This technique does not demonstrate surface immunoglobulin. In case 6 where a presumptive diagnosis was made on cytology, fresh tissue was obtained at operation: B-lymphocytes were demonstrated with monoclonal surface immunoglobulin by immunofluorescence and an alternative immunoperoxidase technique. Also in this case circulating monoclonal B-cells were detected by immunofluorescence. We conclude that these lesions represent an unusually localised form of B-cell lymphoma. Resection is recommended but long-term follow-up is necessary.

## **Significance of unexpectedly large perfusion scan defects in bronchial carcinoma**

DA ELLIS, GJ GIBSON, S NARIMAN, T HAWKINS Large perfusion scan defects are said to indicate that a bronchial carcinoma is likely to be non-resectable because of spread to the mediastinum (Secker Walker and Provan. *Br Med J* 1969;3:327). We performed lung scans in addition to routine pulmonary function and exercise tests in 58 patients undergoing surgery for bronchial carcinoma, and

identified nine in whom perfusion of the affected lung was less than 20% of the total, including four with ipsilateral absence of perfusion. Of these nine patients, five were found to have non-resectable tumours, but four (including one with absent perfusion) had apparently successful resection of the tumour by pneumonectomy. There were no differences in radiological or bronchoscopic appearances or in tumour histology, between the resected and non-resectable cases. Ventilation scans, using  $^{133}\text{Xe}$  and  $^{81\text{m}}\text{Kr}$  in most cases, showed defects matching the perfusion scan. Biopsy of mediastinal lymph nodes revealed metastatic tumour in two of the four resected cases. At review six months after operation all four were well with no clinical or radiological evidence of recurrence. All had returned to normal activities and showed only a small decline in pulmonary function. Of the 49 patients with perfusion of the affected lung  $>20\%$  of the total, six had non-resectable tumours and four others had a positive mediastinal lymph node biopsy. Although an unexpectedly large defect of perfusion increases the likelihood of non-resectability of bronchial carcinoma, our experience suggests that this should not be the sole criterion for regarding patients as inoperable.

#### Endobronchial chondroma: report of four cases

P MITCHELL-HEGGS, M MEREDITH BROWN Endobronchial chondroma is a rare tumour. Four patients, all male, presented with mild respiratory symptoms and radiological appearances of slowly resolving pneumonia or persistent atelectasis. On bronchoscopy, the lesions which were in the large airways were polypoid, well-circumscribed, and with a clearly defined stalk attaching them to intact non-ulcerated bronchial mucosa. Biopsy and cytological examination of sputum, bronchoscopic brushings, and lavage material showed benign endobronchial cells. In all cases the lesions were removed at thoracotomy. The characteristic pathological appearances of chondroma or hamartoma (Liebow. *The lung* 1968) were seen in all cases—a cartilage mass with overlying normal bronchial mucosa. Lung distal to the lesion showed patches of bronchiectasis and lipid pneumonia. No intrapulmonary chondroma or carcinoma were seen. All patients recovered completely with no evidence of recurrence of the lesion. The clinical, radiological, and pathological features of endobronchial chondroma are reviewed. The presence of cartilage in a bronchial biopsy is a strong indication that the lesion is a chondroma. With this lesion conservative surgery, even with minimal sleeve resection, is successful.

We are grateful to Mr Michael Bates for allowing us to include one of his cases.

#### Adenocarcinoma of the bronchus

JR BELCHER Like oat cell carcinoma, adenocarcinoma of the bronchus is a distinct pathological entity. Its proportion of all lung cancers varies considerably throughout the world, but it is usually twice as common in women as in men. It is almost always peripheral. It carries the worst prognosis but one. The proportion among women does not relate to smoking habits; it does among men. The proportion among surgical patients has doubled in the last 30 years in this country. In the USA the proportion now exceeds that of squamous carcinoma. There

is considerable evidence supporting the view that adenocarcinoma has the same relationship to smoking as other bronchial carcinomas.

#### Bronchial stump recurrence after surgery for lung cancer

MR LAW, ME HODSON, SC LENNOX Case notes of 1000 Brompton Hospital patients undergoing pneumonectomy or lobectomy for lung cancer during the period 1966-75 were examined, and 17 patients subsequently developed bronchial stump recurrence of tumour. In each case the patient presented with haemoptysis and tumour was apparent at bronchoscopy and confirmed by biopsy to be of squamous histological type. In only seven cases had tumour on the resected bronchial margin been reported histologically at the time of surgery; no patient had evidence of lymph node metastases. Six of the 17 cases were detected when recurrent tumour was confined to the bronchial stump region, and all were given radiotherapy. Five of these have survived five years after detection of the recurrence with no evidence of tumour on repeat bronchoscopy, and negative biopsies. In 11 cases, tumour recurrence was not detected until it was more extensive (involving main bronchus or lateral tracheal wall). Eight were irradiated with survival ranging from 11 to 46 months, while the three, not irradiated, died within a year. There was no relationship between the interval from surgery to detection of recurrence and survival after detection of recurrence. A further 26 patients from the same period had histologically reported involvement by tumour of the resected bronchial margin at the time of surgery. Twelve of these given postoperative radiotherapy showed no benefit in terms of survival or rate of subsequent bronchial stump recurrence, compared with the 14 non-irradiated patients. Radiotherapy may be curative when given for bronchial stump recurrence of tumour detected at an early stage, although postoperative radiotherapy given because of histological evidence of involvement of the bronchial margin at the time of surgery appears to be of no benefit.

#### Effects of a neodymium-YAG laser on implanted anaplastic carcinomata in mice

P HUGH-JONES, W GARDNER, H HEWITT, M CAROLL, W WHIMSTER Thirty-two mice, each bearing a highly malignant implanted intradermal tumour of 3.5-5.5 mm diameter were irradiated with a Nd-YAG laser using different doses at different times and distances. A clear dose-response curve was obtained, relating laser energy in joules/unit surface area to effect. Below a critical level the tumour grew like non-irradiated control tumours. At higher doses tumours were arrested but then regrew at the control rate. At still higher levels complete cure and skin healing occurred. Histological results from the animal work suggests that the Nd-YAG laser may find a place in the treatment of squamous carcinoma of the bronchus.

#### Control of breathing and respiratory $\text{PCO}_2$ oscillations in patients with airways obstruction

GM COCHRANE, JG PRIOR, CB WOLFF In patients with chronic stable asthma, there is virtually the same adjust-

ment of arterial  $\text{PCO}_2$  ( $\text{Paco}_2$ ) to arterial  $\text{PO}_2$  ( $\text{Pao}_2$ ) as that which occurs in normal subjects acclimatised to high altitude ( $\text{Paco}_2 \text{ expected} = 0.25 \text{ Pao}_2 + 2 \text{ kPa}$ ; Cochrane *et al. Br Med J* 1980;281:705; Wolff. *J Physiol* 1980; 308: 118P). The "normal"  $\text{Paco}_2$  is therefore related to  $\text{Pao}_2$ . Since  $\text{Paco}_2$  when raised indicates impaired respiratory control, an increased ratio of observed to expected  $\text{Paco}_2$  (ventilatory ratio,  $\text{VR}$ ) indicates underventilation. Respiratory  $\text{Paco}_2$  oscillations may contribute to normal ventilatory control and have been recorded indirectly with a fast-response in vivo pH electrode. With this technique, 18 patients with chronic obstructive bronchitis, four with asthma, and 10 with severe clinical emphysema were studied. In vitro  $\text{Paco}_2$  and  $\text{Pao}_2$  were also measured. The  $\text{Paco}_2$  oscillation upslope ( $\Delta\text{Paco}_2/\Delta t$ ) was derived from the in vivo pH oscillation. In patients with chronic obstructive bronchitis and asthma,  $\text{VR}$  strongly correlated with attenuation of  $\Delta\text{Paco}_2/\Delta t$ :  $\text{VR} = -9.53\Delta\text{Paco}_2/\Delta t + 1.88$  ( $r = -0.676$ ;  $p < 0.001$ ). This correlation was absent in patients with clinical emphysema. Unless clinical emphysema is the predominant disorder in patients with airways obstruction, it appears that  $\text{Paco}_2$  oscillations may be necessary for normal ventilatory control.

#### Simultaneous measurement of lung volume and weight

JD ARMSTRONG, EH GLUCK, HAZEL A JONES, RO CRAPO, JMB HUGHES Pulmonary total tissue volume (blood, extravascular water, and dry tissue volume) was measured by finding the difference between the radiographic displacement volume of the thorax ( $\text{RDVT}$ ) and lung gas volume. In 10 healthy upright subjects, simultaneous determinations of  $\text{RDVT}$  and gas volume were made.  $\text{RDVT}$  was determined from postero-anterior and lateral chest radiographs using a computerised modification of the Barnhard method (Barrett *et al. Am Rev Respir Dis* 1976;113:239) and gas volume was measured by helium dilution with each radiographic exposure. At functional residual capacity  $\text{RDVT}$  averaged 4450 ml ( $\pm 450$ ) and gas volume 3610 ml ( $\pm 470$ ); pulmonary total tissue volume by subtraction was  $843 \pm 110$  ml (SD). The density of gas-free lung is 1.05; therefore lung weight was 885 g. In the supine posture at FRC, lung weight would increase by about 100 g because of an influx of blood. The density of the air-filled lung (ml tissue per ml tissue and gas) was  $0.19 \pm 0.03$  (1 SD). This simple method is best suited for detecting the increase in lung weight in fibrotic and granulomatous conditions and in vascular congestion and mild to moderate pulmonary oedema, but it places a premium on the accuracy of the measurements.

#### Simple method of testing respiratory patients on the bicycle

CK CONNOLLY The relationship between symptoms and objective findings in patients with airway obstruction is variable. It is often difficult to relate their performance with simple measures of spirometry. A simple progressive exercise test suitable for such patients is described. Subjects exercise on a bicycle until they are unable to continue against a work load increased logarithmically at 10 second intervals. Spirometry is performed before exercise. Six hundred and five subjects with what was believed to be predominantly obstructive lung disease of all degrees of severity were exercised. Patients with overt cardiac disease

or symptoms suggestive of ischaemic heart disease were excluded. There was an overall correlation of 0.812 between forced vital capacity and maximum work rate attained. Similar correlations were obtained with  $\text{FEV}_1$  but peak flow rate was less satisfactory. Despite the logarithmic increments of exercise there was no advantage in semi-logarithmic analysis. The test has proved of value in assessing objective disability in respiratory subjects.

#### Relationship between pulmonary epithelial permeability and Hbco

BD MINTY, D ROYSTON, JG JONES We have previously shown that symptomless cigarette smokers had an increased epithelial permeability to the chelate  $^{99m}\text{TcDTPA}$  (Jones *et al. Lancet* 1980;1:66). Permeability was expressed as the half time clearance in minutes ( $T_{1/2}$ ) from the lung to the blood of  $^{99m}\text{TcDTPA}$  introduced into the lung as an aerosol (mass median diameter 0.9  $\mu\text{m}$ , geometric SD 3.3). We recently demonstrated a significant reduction in permeability at 24 hr after cessation of smoking (Minty *et al. Br Med J* 1981;1:282). Because of this rapid alteration in epithelial permeability when changing smoking habits the present study was designed to investigate the short-term effects on permeability of changing from middle tar to low tar cigarettes in a single blind study. In 10 subjects smoking middle tar cigarettes the mean  $T_{1/2}$  was  $21.3 \text{ min} \pm 3.3$  (SEM) and carboxyhaemoglobin concentration (Hbco) was  $8.1\% \pm 2.6$  (SEM). Two weeks after changing to low tar cigarettes there was no significant difference in these values; mean  $T_{1/2}$  was  $20.2 \text{ min} \pm 2.5$  (SEM) and Hbco  $7.2\% \pm 2.7$  (SEM). When we examined the relationship between permeability and Hbco in 55 smokers and non-smokers there was a significant ( $p < 0.001$ ) hyperbolic relationship between  $T_{1/2}$  and Hbco. Values for  $T_{1/2}$  ranged from 120 min to 6 min and for Hbco from 0.5% to 12%. This correlation does not imply that carbon monoxide is the underlying cause nor does it exclude other constituents of cigarette smoke from causing the altered epithelial permeability. The hyperbolic relationship between  $T_{1/2}$  and Hbco explains the lack of effect in the group who changed to low tar cigarettes since, with an initial value of Hbco of 8.1%, a much greater reduction in Hbco would be required before a significant improvement in pulmonary epithelial permeability could be expected.

#### Treatment of pulmonary aspergillomata

PH KAY, J JEWKES, KM CITRON, M PANETH Between 1956 and 1980 85 cases of pulmonary aspergillomata were admitted to the Brompton Hospital. Diagnosis was based on chest x-rays and raised aspergillus precipitins. Sixty-six patients presented with recurrent haemoptysis, 10 had malaise, and nine were asymptomatic. Forty-five patients were treated medically initially, 28 receiving systemic or local anti-fungal agents. Twenty-four patients improved symptomatically, although the aspergilloma was eradicated in only one case. Two patients died, while nine required elective surgery. Of the 49 patients treated surgically 41 with localised lung disease underwent resection with an 8% mortality. Five patients experienced major complications requiring additional surgery, and two developed recurrent aspergillomata. Five-year survival was

84% after excisional surgery and 60% after medical treatment. All 16 patients presenting with major haemoptysis (greater than 150 ml/24 hr) settled initially with conservative management. One of the nine patients treated surgically died, compared with two of the seven patients treated medically. In eight patients with generalised lung disease resection was considered too hazardous. A cavernostomy was performed and the aspergilloma evacuated. Four patients died. The remaining four underwent intracavity infusion of natamycin and remain well a mean of seven years later.

#### Allergic bronchopulmonary aspergillosis causing lung collapse in non-asthmatic patients

KE BERKIN, DRH VERNON, JW KERR Allergic bronchopulmonary aspergillosis (ABPA) classically occurs as a complication of asthma with "fleeting shadows" on the chest radiograph. Five patients with lung collapse, thought to be caused by bronchial carcinoma, were referred for bronchoscopy. The unusual finding of thick white material obstructing major bronchi led to further investigations confirming the diagnosis of ABPA. No patient had a past history of asthma; one had hay fever. All responded rapidly to physiotherapy, steroids, and anti-fungal drugs, alone or in combination. Lung collapse caused by ABPA in non-asthmatic patients is unusual. Diagnosis is straightforward, and depends on demonstration of precipitins, positive skin tests, and isolation of *Aspergillus fumigatus* from the sputum. It is important that physicians and bronchoscopists should recognise ABPA as a cause of lung collapse, because of its rapid response to treatment and good prognosis.

#### Sarcoidosis primarily affecting the nasopharynx and sinuses

JK BRENNAND, RS MCNEILL Two middle-aged patients, a man and a woman, presented with symptoms of sinusitis and nasal obstruction. Investigations showed that these were caused by extensive granulomatous lesions histologically compatible with sarcoidosis. Cervical lymph node involvement also occurred. Pulmonary symptoms were minimal or non-existent but radiologically hilar adenopathy and pulmonary infiltration eventually developed. There was a good response to treatment with prednisolone in respect of the nasal symptoms.

#### Allergic aspergillosis of the maxillary sinuses

JW MILLAR, A JOHNSTON, D LAMB Fungal infections of the paranasal sinuses are relatively unusual and in this country are usually attributed to colonisation by *Aspergillus* species after prolonged broad spectrum antibiotic therapy. This explanation does not account adequately for the condition either in terms of the clinical presentation or the pathological and immunological findings, and it is surprising that a direct comparison between fungal involvement of the sinus and the well-recognised syndromes associated with *Aspergillus fumigatus* involving the rest of the respiratory tract has not been made previously. Five patients with *Aspergillus* infection of the maxillary sinuses are described. All presented with symptoms of chronic sinusitis. One had pre-existing allergic broncho-

pulmonary aspergillosis and two had evidence of airways obstruction. Details of radiological, immunological, and pathological findings will be presented. The presence of marked immediate type hypersensitivity to *Aspergillus fumigatus* and the similarities of the histological appearances of material from the sinus and the expectorated plugs from cases of allergic bronchopulmonary aspergillosis suggest the two conditions are comparable. We suggest that the entity "allergic aspergillosis of the paranasal sinuses" exists.

#### Airways obstruction in myasthenia gravis

DJ SHALE, DJ LANE, CJF DAVIS A review of 21 patients with myasthenia gravis revealed six with symptoms of airways obstruction. Of these, three were atopic with positive skin prick test responses. The others were or had been cigarette smokers. All took regular anti-acetylcholinesterase therapy. A further patient had asymptomatic airways obstruction ( $FEV_1/FVC$  66%, two hours after pyridostigmine). In six patients assessments were made of the effect of anti-myasthenic therapy on airways function. In a double-blind fashion either placebo or the anti-cholinergic bronchodilator ipratropium bromide (72 mcg) was given by inhalation together with the anti-myasthenic therapy on two consecutive days. Specific airways conductance (sGaw) fell significantly after the placebo inhaler to  $75 \pm 5.6\%$  of baseline sGaw at two hours (mean  $\pm$  SEM,  $p < 0.025$ ). A significant increase in sGaw occurred after ipratropium bromide to  $178 \pm 19\%$  of baseline sGaw at two hours ( $p < 0.005$ ). Reciprocal changes in FRC and RV occurred after ipratropium bromide. Thus acetylcholinesterase inhibitor therapy caused a significant increase in airways resistance in myasthenic patients with airways obstruction and this effect was completely reversed by the inhalation of ipratropium bromide.

#### Hypoventilation is common, but sleep apnoea rare, in transient nocturnal hypoxaemia of blue and bloated bronchitis

JR CATTERALL, NJ DOUGLAS, PMA CALVERLEY, C SHAPIRO, V BREZINOVA, DC FLENLEY Recurrent transient hypoxaemia during nocturnal sleep commonly occurs during REM sleep in "blue and bloated" (BB) patients with chronic bronchitis and emphysema, but is rarely seen in "pink and puffing" (PP) patients. In 20 normal subjects, (10M, 10F mean age 52 yr) the lowest  $SaO_2$  asleep was 71-95%; whereas in seven PP (five M, two F, mean age 61 yr,  $FEV_{1.0}$  0.5-0.9 l, awake  $Pao_2$  67-80 mmHg,  $Paco_2$  27-40 mmHg) the lowest  $SaO_2$  asleep was 70-89%; and in 13 BB (seven M, six F, mean age 57 yr;  $Pao_2$  40-58 mmHg,  $Paco_2$  43-61 mmHg, PAP 21-59 mmHg, red cell mass 41-55 ml/kg, all awake) the lowest  $SaO_2$  asleep was 30-75%. Of the 40 hypoxaemic episodes (HE) in sleep, (HE =  $SaO_2$  falling  $> 10\%$  from stable sleep level) in BB or PP, 29 episodes (29/36 in BB and 3/4 in PP) occurred with a breathing pattern of central hypopnoea; obstructive sleep apnoea did not occur in these patients. However, in the 20 normal subjects three of the four HE occurred in obstructive apnoea. In 10 BB the greatest fall in measured  $Pao_2$  was on average 11.2 mmHg, whereas  $Paco_2$  only

rose by 4.2 mmHg, suggesting  $\dot{V}_a/\dot{Q}$  imbalance became worse in central hypopnoea. As the normal subjects and PP had normal  $\text{Sao}_2$  awake, calculated falls in  $\text{Pao}_2$  (from observed  $\text{Sao}_2$  changes, assuming pH values) were nonetheless similar in BB ( $\Delta\text{Pao}_2=16.8$  mmHg), PP ( $\Delta\text{Pao}_2=23.4$  mmHg) and normal subjects ( $\Delta\text{Pao}_2=27.9$  mmHg). Furthermore the cumulative duration of sleep apnoea and hypopnoea in each patient was no different in the three groups. BB does not appear to be a sleep apnoea syndrome.

#### Hormone and metabolic studies during cor pulmonale and after recovery

PD A SEMPLE, GH BEASTALL, WS WATSON, R HUME We have demonstrated low serum testosterone levels in hypoxic bronchitic subjects (Semple *et al. Clin Sci* 1980;58:105) in addition to low total body potassium (TBK) values (Semple *et al. Thorax* 1978;33:734). Since it has been suggested that fluid shifts occur between body compartments in cor pulmonale failure (Campbell *et al. Clin Sci* 1975;49:323), we decided to assess whether endocrine and metabolic changes occur between acute cor pulmonale and recovery several months later. Between the acute illness and recovery there was a significant rise in  $\text{Pao}_2$  ( $p<0.01$ ) and a commensurate rise in serum testosterone ( $p<0.01$ ) and serum FSH ( $p<0.01$ ). No great change was noted in total body water though extracellular water tended to fall and intracellular water rose significantly ( $p<0.05$ ). TBK values were low in cor pulmonale ( $p<0.005$ ) and there was an unexpected and significant drop with recovery ( $p<0.05$ ). These findings support our view that hypoxia suppresses the hypothalamic-pituitary-testicular axis. They confirm Campbell and colleagues' findings that oedema in cor pulmonale is partly the result of shift of fluid from the intracellular to the extracellular compartment associated with loss of muscle mass, and suggest that such body changes may be caused by anabolic steroid fluctuations. They confirm our unexplained finding of potassium depletion in cor pulmonale which surprisingly remains low after recovery.

#### Early effects of intravenous terbutaline on cardiopulmonary function in patients with chronic bronchitis and cor pulmonale

RM JONES, RA STOCKLEY, JM BISHOP Halmagyi and Cotes (*Clin Sci* 1959;18:475) suggested that  $\beta$ -adrenergic agents may increase venous admixture in patients with chronic airflow obstruction resulting in further systemic arterial hypoxaemia. Stockley *et al. (Thorax* 1977;32:601) demonstrated a small increase in venous admixture 40 mins after intravenous terbutaline although arterial  $\text{Po}_2$  ( $\text{Pao}_2$ ) was unaltered. They noted that any change in  $\text{Pao}_2$  would be greatest shortly after injection when circulating drug levels would be highest. This study was designed to assess cardiopulmonary changes five and 35 mins after an intravenous bolus of terbutaline (0.25 mg) in 10 clinically stable patients with irreversible airflow obstruction (mean  $\text{FEV}_1=0.70$ ;  $\pm 0.20$  (SE) litres) during right heart catheterisation. Cardiac index rose from a mean resting level of  $2.17\pm 0.15$  to  $3.36\pm 0.26$  l/min/m<sup>2</sup> (mean  $\pm$  SE) ( $p<0.005$ ) and then fell to  $2.74\pm 0.16$  l/min/m<sup>2</sup> which was still higher than the resting value ( $p<0.05$ ).

This was accompanied by a rise in alveolar ventilation ( $p<0.001$ ) at five minutes which returned to resting levels by 35 mins. There was no significant change in venous admixture.  $\text{Pao}_2$  rose from  $7.6\pm 0.5$  kPa at rest to  $8.0\pm 0.4$  kPa at five min ( $p<0.05$ ). In view of this unexpected finding,  $\text{Pao}_2$  was measured at minute intervals after terbutaline in a further eight patients (mean  $\text{FEV}_1=0.64\pm 0.24$  litres).  $\text{Pao}_2$  rose at one minute reaching a maximum at four minutes (resting= $8.5\pm 0.6$  kPa; 4 min= $9.1\pm 0.4$  kPa;  $p<0.01$ ) and thereafter returned to resting values over 15 minutes. This was accompanied by a rise in ventilation. It is concluded that intravenous terbutaline in this dose does not adversely affect cardiopulmonary function in this group of patients. The transient rise in  $\text{Pao}_2$  seen after the drug may be caused by a stimulant effect on ventilation perhaps via the hypoxic drive.

#### Glandular tuberculosis in Asians: is clinical diagnosis sufficient?

PJ STANLEY, PR FARROW, DA JONES, JB COOKSON, JM WALES Opinion remains divided on the necessity for lymph node biopsy in patients suspected of having tuberculous lymphadenitis. Summers and McNicol (*Br J Dis Chest* 1980;74:369) suggest that it is safe to start treatment, deferring biopsy for those who do not respond satisfactorily. Most glandular tuberculosis occurs in immigrants. We reviewed 53 lymph node biopsies in Asians with a clinical diagnosis of tuberculosis. Thirty-eight confirmed tuberculosis on histology or culture. Three showed non-specific inflammation, but were treated for tuberculosis regardless. Twelve were non-tuberculous, and included squamous carcinoma (two), adenocarcinoma (one), oat cell carcinoma (one), Hodgkin's lymphoma (one), sarcoid (one), branchial cyst (one), and non-specific inflammation (five). Six of the 53 were biopsied during treatment because of clinical doubt. Four biopsies confirmed tuberculosis, one revealed Hodgkin's, and one a branchial cyst. The Heaf test was a poor discriminator. Thirty-one of the 38 patients with proven tuberculosis had documented Heaf tests; three were negative and three low-grade positive. In the 12 with other diagnoses, there were seven strongly positive Heaf tests, three weakly positive, and two negative. We submit that routine superficial lymph node biopsy leads to a clinically important change of management for a substantial number of these patients.

#### Lung fibrosis in polyvinyl chloride workers

AM HUNTER, JC WAGNER, N JOHNSTON, A SEATON Polyvinyl chloride (PVC) is produced as granules, some of which may fall into the respirable size range. Animal experiments have shown that some formulations of PVC may cause a bronchiolar and alveolar granulomatous reaction, though our own studies with pure PVC have not confirmed this. A detailed epidemiological study of PVC workers has shown minor radiographic and physiological changes related to estimates of dust exposure (Soutar *et al. Thorax* 1980;35:644). Two individual cases of lung fibrosis in PVC workers have also been reported, though causality has not been established (Szende *et al. Med Lav* 1970;6:433, Arnaud *et al. Thorax* 1978;33:19). We have reviewed the chest radiographs, physiology, and lung

histology of six PVC production workers, all of whom had been exposed also to the monomer (VCM). Three presented for investigation of radiological abnormality, one having been discovered in an epidemiological survey, and three had died of VCM induced liver disease. None had significant respiratory symptoms. Lung transfer factor was reduced in only one of the three with abnormal radiographs. All six lungs showed similar histological appearances, with an inflammatory interstitial infiltrate. PVC granules and other dust particles were demonstrated in the three in whom electron microscopy was performed.

### Angler's asthma

RA STOCKLEY, S HILL, R DREW Seasonal asthma in an angler was described by Buisseret in a letter (*Lancet* 1978; 1:668). He noted that the symptoms disappeared after the patient changed bait. We describe a 41-year-old angler who experienced asthmatic symptoms only while fishing with live maggots. Sneezing, itching, and urticaria started within one hour of starting to fish but wheeze developed some six to eight hours later. On fishing days PEF fell, with lowest values occurring during the night 16 to 18 hours after fishing. The subject had negative prick tests to common allergens, normal immunoglobulin concentration, and a slight eosinophilia. A water soluble extract of maggots gave a brisk immediate reaction to prick testing but the swelling and erythema persisted for three days suggesting a dual response. Further examination of the patient's serum by passive haemagglutination showed the presence of a precipitating antibody of the IgG<sub>1</sub> subclass. This antibody was not detected in asymptomatic fishermen who use live maggots as bait.

### Some aspects of asthma in the desert

R ELLUL-MICALLEF Kuwait, situated in the north-west corner of the Arabian Gulf, has an arid climate with very hot dry summers and mild winters. The prevailing winds are north-westerlies which frequently raise sandstorms especially in summer. Before the mid-1950s allergy was not considered to be a problem. Since then it has become a major cause of morbidity; 18% of the population are reported to suffer from its manifestations. In 1966 an Allergy Unit was set up to which most patients with suspected bronchial asthma are referred. Over the past two years, 1000 of these patients have been carefully studied. Extrinsic atopic asthma was present in about 74% and was frequently associated with allergic rhinitis (63%). Allergic conjunctivitis, generalised urticaria, and eczema were also not infrequently present. Sinusitis was present in 13%. The pollen of the tree *Prosopis juliflora*, the weed *Chenopodium album*, and *Cynodon dactylon* (Bermuda grass) appeared to be the principal causative allergens. Most cases occurred between April and September. Chronic intractable cough, with or without dyspnoea, in the absence of wheezing, was not an uncommon presentation. Of the non-Kuwaiti patients, 10% had asthma before coming to Kuwait, 30% developed the condition after three years, and 90% within 10 years. Climatic factors, including sudden changes in temperature and humidity between air-conditioned homes and the outside environment, and the unaccustomed exposure to relatively high pollen concentrations after a determined afforestation

programme started in 1950, appear to account for the high local prevalence of this condition.

### Circulating $\beta$ -adrenoreceptor blocking factor in asthma

GS BASRAN, AJ BALL, JM HANSON, M TURNER-WARWICK It has been proposed that in asthma  $\beta$ -adrenoreceptor function is impaired not only in the lung but throughout the body (Szentivanyi. *J Allergy* 1968;42:203). Such dysfunction could result from intrinsic defects in the  $\beta$ -receptor mechanism or may be attributed to circulating factors which interfere with the functional binding of catecholamines to the  $\beta$ -receptor. With the recent development of labelled high affinity  $\beta$ -receptor antagonists, radio-ligand binding study has become a routine procedure so that it is now possible to screen sera for such circulating  $\beta$ -receptor blocking factors. We measured the binding of the labelled  $\beta$ -receptor antagonist <sup>125</sup>I-Iodohydroxybenzyl pindolol (<sup>125</sup>I-HYP) to guinea-pig lung membrane preparations. Inhibition of this binding by excess unlabelled propranolol (10  $\mu$ M) was used to estimate specific  $\beta$ -receptor binding. The effect of sera from 24 normal and 76 asthmatic subjects on the specific binding was studied, and the results compared with those for a reference serum (commercial serum). The results are expressed as relative binding. The mean value of relative binding for the asthmatic group is significantly ( $p < 0.001$ ) lower than that for the normal group. Furthermore, in the initial screen low values (outside the 99% confidence limits for the normal group) were observed with 19 out of 76 asthmatic sera. To date, seven of these have been confirmed on at least two separate occasions and the rest are still under investigation. This difference between normal and some asthmatic sera could be caused by the presence of a circulating  $\beta$ -receptor blocking factor, although the lack of a facilitatory factor has not yet been excluded. The nature of this circulating factor, and its clinical significance, is under investigation.

### Psychologically induced bronchoconstriction: is it caused by airway cooling?

RA LEWIS, MN LEWIS, AE TATTERSFIELD Asthmatic subjects may bronchoconstrict after inhaling saline, when told the inhalations cause bronchoconstriction (McFadden *et al. Psychosom Med* 1969;31:134). This effect was attributed to suggestion, but alternatively could have been caused by airway cooling, since asthmatic patients bronchoconstrict after inhaling saline at 5 and 20°C, but not at 37°C, 100% saturation (Lewis and Tattersfield. *Clin Sci* 1980;59:12P). We have reassessed the effect of suggestion on the airway response to inhaled solutions. Twelve normal and 30 asthmatic subjects took part in a randomised double-blind study, measuring airway response as specific conductance (sGaw) with an on-line microprocessor. sGaw was measured before and after 10 successive inhalations of saline, followed by five inhalations of isoprenaline (16 to 250  $\mu$ g/ml). Subjects were given written statements suggesting (1) the first five solutions contained doubling concentrations of either a bronchoconstrictor or bronchodilator; (2) the next five solutions would have the reverse effect; (3) the first four doses of isoprenaline would have no effect, while the last dose would cause bronchodilation. There was no change

in sGaw after saline in normal subjects while eight of 30 asthmatic subjects suffered bronchoconstriction (20% reduction in sGaw); this was unrelated to the nature of the suggestion. When the study was repeated in these eight subjects at 37°C, 100% saturation, bronchoconstriction was abolished. Suggestion did not affect the response to isoprenaline in normal or asthmatic patients. We conclude that the bronchoconstriction in asthma, previously attributed to suggestion, is caused by a cooling effect of saline on the airways.

#### Duration of protection from exercise-induced asthma by salbutamol and comparison with reproterol

CMB HIGGS, G LASZLO Little is known about the duration of protection from exercise-induced asthma (EIA) by salbutamol. We studied this in six stable asthmatic patients (three male, three female) aged 16-32 years with proven EIA, an FEV<sub>1</sub> >80% predicted normal and varying <10% on trial days. The effect of a standard six-minute treadmill exercise test on peak expiratory flow rates (PEFR) was measured on entry to the study, and then repeated under the same conditions on separate days at intervals of one, two, four, or six hours after inhalation of 200 µg salbutamol. FEV<sub>1</sub> was measured at hourly intervals. Protection from EIA

$$\left( \frac{\% \text{ fall control PEFR} - \% \text{ fall test PEFR}}{\% \text{ fall control PEFR}} \times 100 \right)$$

was defined as being lost when it fell below 75%. The time at which this occurred ( $t < 75\text{PS}$ ) was determined for each subject. A further exercise test was performed at  $t < 75\text{PS}$  after inhalation of 1 mg reproterol—a new  $\beta_2$  adrenergic xanthine derivative. Duration of protection from EIA by salbutamol varied from one to >four hours. Reproterol gave greater protection at  $t < 75\text{PS}$  ( $p < 0.01$ , paired  $t$  test). There was no relation between duration of bronchodilator effect on FEV<sub>1</sub> and duration of protection from EIA.

#### The refractory period in hyperventilation-induced asthma

NM WILSON, PJ BARNES, H VICKERS After exercise-induced bronchoconstriction, there is a refractory period lasting up to two hours during which a second exercise test provokes less bronchospasm. This may represent the time necessary for repletion of mast cell mediators released during exercise. The initiating stimulus for exercise-induced asthma is airway cooling produced by hyperventilation, although whether this produces bronchoconstriction by vagal reflex or by mediator release is undetermined. We have examined whether a refractory period can be demonstrated using paired isocapnic hyperventilation challenges. Seventeen extrinsic asthmatic subjects (aged 10-38 yr) performed an isocapnic hyperventilation test and a repeat test 40 min later with matched ventilation. The maximum fall in peak expiratory flow was  $40.5 \pm 3.3\%$  (mean  $\pm$  SEM) in the first test and significantly less ( $p < 0.02$ ) in the second ( $27.2 \pm 4.8\%$ ), although ventilation was not significantly different ( $40.4 \pm 1.7$  l/min test 1;  $40.2 \pm 1.8$  l/min test 2). Analysis of individual subjects showed two groups: nine demonstrated refractoriness, but eight did not. Preliminary data show that cholinergic blockade (ipratropium bromide 80 µg inhaled) prevented hyperventilation-induced

bronchoconstriction in five out of six subjects in the "non-refractory" group, suggesting that vagal reflex mechanisms are involved. But in the "refractory" group only one out of eight subjects was blocked, indicating that mediator release may be important.

#### Mechanism of exercise-induced asthma

TH LEE, L NAGY, MJ WALPORT, AB KAY A high molecular weight, heat stable, neutrophil chemotactic factor (NCF) has been described in the circulation of patients with bronchial asthma after inhalation of specific antigen (Atkins *et al.* *Ann Intern Med* 1977;86:415). We have identified a comparable mediator in the serum of 13 atopic asthmatic subjects after treadmill exercise (NCF<sup>EX</sup>). Peak activity was detected at 10 min and returned to pre-challenge values by one hour. No NCF activity was found in the sera of three normal atopic or four normal non-atopic individuals performing the same task. NCF<sup>EX</sup> had a similar time course of release to NCF provoked by specific antigen (NCF<sup>AG</sup>) and the appearance of circulating NCF<sup>EX</sup> and NCF<sup>AG</sup> closely paralleled the fall in PEFR or FEV<sub>1</sub>. Histamine challenge in atopic asthmatic patients, at concentrations giving a comparable change in PEFR or FEV<sub>1</sub> to that evoked by exercise or inhaled antigen, was not associated with the appearance of circulating NCF. NCF<sup>EX</sup> release was inhibited by previous administration of disodium cromoglycate (DSCG). NCF<sup>EX</sup> and NCF<sup>AG</sup> eluted as a single peak when applied separately to columns of Sephadex G-200 and both had an estimated molecular size of approximately 750,000 daltons. These experiments indicate that NCF<sup>EX</sup> and NCF<sup>AG</sup> are probably identical and raise the possibility that mediators of hypersensitivity play a role in the pathogenesis of exercised-induced asthma in atopic subjects.

#### Circadian variation in adrenergic responses in asthmatic patients who develop nocturnal wheeze

PJ BARNES, GA FITZGERALD, CT DOLLERY To determine whether circadian variations in adrenergic responsiveness might underlie nocturnal asthma we investigated the cardiovascular, airway, and venous plasma cyclic AMP response to graded infusions of 1-adrenaline (0.01, 0.03, 0.075 µg kg<sup>-1</sup> min<sup>-1</sup> for 10 min) at four-hourly intervals over a 24-hour period in five extrinsic asthmatic men (aged 22-35 yr). Baseline peak expiratory flow (PEF), blood pressure, heart rate, and plasma cyclic AMP showed a significant circadian variation with peak values at 1600 hr and trough values at 0400 hr. The  $\beta_2$ -adrenoceptor mediated increases in PEF and cyclic AMP were similar at all times, although "adrenergic responsiveness", determined by the slope of the line relating response to log (infused adrenaline concentration), was greater at 0400 hr than at 1600 hr because of the lower baseline values at night. Cardiovascular responses to adrenaline infusions did not differ significantly over the 24-hour period, however. On the second study day bronchodilator responses to inhaled adrenaline (0.56 mg) were determined at the same times. PEF after adrenaline inhalation was not significantly different at 0400 hr compared with 1600 hr in spite of the lower baseline value. We conclude that there is no significant change in adrenoceptor-mediated responses in

asthma and that adrenoceptor dysfunction is not important in the pathogenesis of nocturnal wheezing.

#### Plasma levels of slow reacting substance of anaphylaxis (SRS-A) in asthma patients

BJ HUTCHCROFT, RJ DAVIES Evidence that allergic mechanisms are important in asthma remains circumstantial. Plasma histamine levels are raised in the asthmatic population but no convincing histamine release has been demonstrated in man during induced asthma attacks. Levels of substances chemotactic for neutrophils are raised during acute antigen-induced asthma but not during post-exertional asthma. This study was designed to look at circulating levels of SRS-A, another potential mediator of allergic reactions, in the plasma of control and asthmatic patients, both when well and acutely ill with their disease and during exercise testing. Venous blood (20 ml) was obtained from the patients (arterial samples from the acutely ill asthma patients). The plasma fraction was separated and subjected to an 80% ethanol extraction procedure with subsequent evaporation to dryness. The residue was reconstituted with 1 ml of distilled water and assayed for SRS-A activity using a guinea-pig ileum assay with rat peritoneal cell SRS-A as a standard. The results are shown in the following table with levels of SRS-A activity expressed as units/ml of plasma. There were no consistent changes in the levels of circulating SRS-A in patients showing post-exercise bronchoconstriction. The highest level of SRS-A activity 25 u/ml was seen in a man with systemic mastocytosis. This study failed to demonstrate detectable increases in circulating SRS-A in the plasma of patients with asthma.

Group	Number	Mean level	Range
Control subjects	10	4	1.5-10
Stable asthma patients	15	4	0.5-10
Acute asthma patients	4	2	0.6- 6

#### Administration of a beta-agonist: comparison of three techniques

MJ CUSHLEY, RA LEWIS, DJB CRAGG, IL JACKSON, AE TATTERSFIELD The dose of beta-agonist used in nebulisers at home may be 50 times greater than the recommended dose for metered aerosols. This increased dose might be necessary if nebulisation is less efficient at delivering the drug to the airways. This study compares the bronchodilator response in a dose-response manner to the same doses of beta-agonist given by nebuliser, metered aerosol, and metered aerosol with pear-shaped extension tube (pear) to determine the relative efficiency of the three methods of administration. Eight asthmatic and eight normal subjects inhaled increasing doses of terbutaline on separate days in a randomised double-blind study, using the three different techniques. The bronchodilator response was assessed as change in sGaw and FEV<sub>1</sub>. The response to terbutaline given by aerosol plus pear was greater than the response given by metered aerosol alone or nebuliser. The dose-response curve for aerosol plus pear was significantly displaced to the left, while those for the nebuliser and the metered aerosol did not differ significantly from each other. The results suggest that a dose from a metered

aerosol with pear is at least twice as effective as that from a metered aerosol alone. Any difference in efficiency between metered aerosol and nebuliser is small.

#### Effect of chronic salbutamol treatment on the airway response to inhaled prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) in asthmatic patients

EH WALTERS, M BEVAN, BH DAVIES PGE<sub>2</sub> may be involved in normal homeostasis of the airways. It has been suggested that in asthmatic patients there is a variable response to inhaled PGE<sub>2</sub>. We have used dose-response curves to investigate the pharmacology of PGE<sub>2</sub> in asthmatic airways in more detail. Cumulative inhalation dose-response curves were constructed on two separate occasions in eight stable asthmatics on no regular therapy. Doses ranged from 10 to 400 µg given at 15 min intervals via a Wright's nebuliser. Airway responses were measured as changes in sGaw. Whereas normal subjects show uniform dose-related bronchodilatation to PGE<sub>2</sub>, six of the asthmatic patients had a biphasic response on at least one occasion. In the majority of patients there was a level of sGaw above which PGE<sub>2</sub> was bronchoconstrictor and below which it was dilator. The mean maximum percentage increase from baseline sGaw was 63% (SE ± 10%) with the mean final sGaw reading being 55% (SE ± 13%) above baseline. After regular salbutamol therapy (400 µg inhaled qid) for four weeks the mean PGE<sub>2</sub> dose-response curve was markedly shifted towards bronchodilatation (p < 0.005) and this was significant at all doses. This stabilisation of PGE<sub>2</sub> action towards normal may be an important aspect of regular salbutamol therapy.

#### Does inspiratory flow rate affect bronchodilator response to an aerosol β<sub>2</sub> agonist?

P LAW FORD, D MCKENZIE Instruction leaflets supplied with pressurised bronchodilator aerosols give contradictory information on inhaler technique. Some advise a slow, deep inhalation whereas one advises patients to inhale "deeply and suddenly". The effect of inspiratory flow rate on bronchodilator response was studied in 21 patients with reversible airways obstruction, with mean initial FEV<sub>1</sub> of 47% predicted. They attended on four separate visits and omitted bronchodilator therapy for nine hours beforehand. After baseline measurements of expiratory flow they received one puff (200 µg) fenoterol or placebo, at a fast or slow inspiratory flow rate, according to a latin square plan. The inhaler unit was placed in series with a spirometer attached to a flow-volume differentiator and penrecorder. They inhaled from RV to TLC and held their breath for 10 seconds. Subsequent measurements of expiratory flow were made at 10, 30, and 60 minutes. There was no significant difference in mean initial FEV<sub>1</sub> on any treatment day. Mean inspiratory flow was 192 l/min on fast days and 64 l/min on slow days. The response, expressed as placebo subtracted mean % increase in FEV<sub>1</sub>, at 10 minutes was 18.2 ± 24% with fast inspiratory flow and 30.4 ± 25% for slow (p < 0.05, Wilcoxon rank sum test); at 30 minutes 21.7 ± 23% for fast flow and 31.3 ± 24% for slow (NS); at 60 minutes 20.5 ± 18% at fast flow and 25.3 ± 29% for slow (NS). Instructions issued with bronchodilator aerosols should advise a slow inspiratory flow rate.



# **Aerosol salbutamol versus oral slow release aminophylline in the treatment of nocturnal asthma**

ARL PENKETH, D JOHNSON, MR HETZEL, TJH CLARK, D BEL-LAMY, GM COCHRANE We have compared the relative merits of sustained-release aminophylline and aerosol salbutamol in the control of nocturnal asthma. Twelve asthmatic patients with a history of nocturnal attacks, and an overnight fall in PEFR of at least 25% were recruited. In a randomised, double-blind, cross-over study they were given twice daily trial aerosols and tablets of which one or both contained placebo. Weeks 1-3 assessed 400 µg salbutamol rotacap bd, 225 mg aminophylline (Phyllocontin) bd, or both placebo tablets and aerosol. Weeks 4-6 compared 800 µg salbutamol bd, 450 mg aminophylline bd, and double doses of placebo. Patients kept diary cards of PEFR and additional bronchodilator consumption. Plasma theophylline levels were measured on the last night of each week's treatment. Only the higher doses of both active drugs reduced the overnight fall in PEFR compared with placebo ( $p < 0.05$ ). Although these doses achieved better control of nocturnal symptoms they did not reduce the variation in PEFR during the day. Plasma theophylline levels were suboptimal in most cases; nevertheless aminophylline significantly reduced the number of nocturnal attacks, without side-effects. There were marked differences in individual responses to both drugs. We conclude that standard doses of bronchodilator drugs may prove inadequate in nocturnal asthma. Dosage appears to be more important than the choice of drug or route of administration.

## **General anaesthesia for rigid bronchoscopy—how safe?**

DJ GODDEN, RF WILLEY, RJ FERGUSSON, GK CROMPTON, IWB GRANT Intravenous general anaesthesia using oxygen venturi ventilation superseded local anaesthesia for rigid bronchoscopy at the Northern General Hospital in 1974. Since then, over 1400 examinations have been carried out using this technique with no associated deaths and an unexpectedly low complication rate considering the high anaesthetic risk presented by many patients. In a detailed prospective study of 100 consecutive bronchoscopic examinations, no serious complications occurred. Minor complications included one adverse reaction to alphaxalone-alphadolone acetate (Althesin), one episode of prolonged laryngeal spasm after removal of the bronchoscope, and a high incidence of postoperative muscle pain related to the administration of suxamethonium. Neuromuscular blockade using suxamethonium alone caused pain in 40% of patients, but non-depolarising and depolarising agents used in combination did so in only 20% ( $p < 0.025$ ). Serial arterial blood gas sampling carried out in 10 patients confirmed that this technique of ventilation achieved adequate oxygenation without carbon dioxide retention throughout the procedure. In the period after removal of the bronchoscope, however, eight of 10 patients developed varying degrees of hypercapnia and respiratory acidosis. With adequate safeguards such as pre-oxygenation and close supervision after bronchoscopy, general anaesthesia using oxygen venturi ventilation allows rigid bronchoscopy to be performed safely and quickly even in patients with poor respiratory function.

Side-effects can be minimised by the use of appropriate anaesthetic and neuromuscular blocking agents.

## **Effect of fibreoptic bronchoscopy on transcutaneous oxygen tension**

BJ GRAY, MJ TOBIN, JA HUGHES, K HASSANEIN, J COSTELLO We monitored transcutaneous oxygen tension ( $tcPo_2$ ) in 30 patients undergoing fibreoptic bronchoscopy (FOB). In 21 patients breathing air mean  $tcPo_2$  was  $8.65 \text{ kPa} \pm 1.65$  and no significant change occurred during the application of topical anaesthesia or during routine bronchoscopy. Seventeen patients had a lung washout performed using a 20 ml aliquot of saline and this produced no change in  $tcPo_2$ . Eleven patients had a second washout in the same lobe, resulting in a fall in  $tcPo_2$  of  $1.7 \text{ kPa} \pm 1.7$  ( $p < 0.01$ ). Nine patients received oxygen at two litres per minute by nasal cannula. After two washouts in the same lobe, the  $tcPo_2$  was still higher ( $1.7 \text{ kPa} \pm 2.0$ ,  $p < 0.05$ ) than the baseline  $tcPo_2$  in the same patients breathing air. Continuous  $tcPo_2$  monitoring provides a simple, non-invasive method, reflecting both the magnitude and duration of changes in arterial oxygen tension, with greater precision than arterial sampling. Forty ml saline was the minimum cumulative volume, used in one lobe to cause significant falls in  $tcPo_2$ . Low flow oxygen during lung washouts maintained the  $tcPo_2$  above baseline levels.

## **Hiatal hernia with primary oesophageal spasm**

GAL WILKINSON, IP ADAMS, HR MATTHEWS Diffuse oesophageal spasm as a "primary" condition is now well recognised. Spasm can also occur in association with a hiatal hernia, but is then generally assumed to be secondary to gastro-oesophageal reflux, whether confirmed or not. In the last four years we have identified four patients with coexisting hernia and spasm, in whom there was no evidence of reflux on prolonged oesophageal pH recording. Three patients were men and one a woman, aged 60-73 years. Barium studies showed a definite hiatal hernia with inco-ordinated contractions in all patients. None had oesophagitis at endoscopy. Oesophageal manometry confirmed disturbed motility in all; lower sphincter pressures were low in two and normal in two. Continuous 16-hour oesophageal pH recordings showed no abnormal reflux in any patient. In all cases symptoms were severe and treatment was by extended longitudinal myotomy with an anti-reflux procedure. These findings indicate that there is a group of patients with both hernia and "primary" spasm who are quite distinct from those with diffuse spasm but no hernia, and those who have proven reflux with "secondary" spasm. The recognition of these patients is important in that repair of the hernia alone will fail to relieve the symptoms which are caused primarily by disordered oesophageal motility.

## **A conservative surgical method for reflux stricture associated with short oesophagus**

K MOGHISSI Conservative surgery of perioperative dilatation of a stricture coupled with hiatal hernia repair is now an accepted method of treatment in reflux stricture of the oesophagus. This however cannot be applied when the oesophagus is short and the hernia cannot be reduced.

Therefore many surgeons advocate radical surgery of resection and reconstruction. This paper describes a conservative surgical method which we have used in 38 patients. Between September 1970 and March 1980, 86 patients with reflux stricture and short oesophagus were operated on. Forty-eight had resection and reconstruction using stomach, jejunum, or colon. In 38 patients conservative surgery was used. This consisted of transthoracic exposure of the oesophagus and stomach, transgastric retrograde dilatation of the stricture, coupled with modified intrathoracic Nissen fundoplication. There were two hospital deaths (5.2%). Patients were followed up from six months to nine years (mean 57 months). Four patients complained of fullness and reflux up to six months after surgery. One patient required postoperative dilatation, no patient required further surgery. Conservative surgery should be considered in strictures with short oesophagus, particularly in patients with poor general condition.

#### Effect of physiotherapy on postoperative pulmonary function and complications

CG MORRAN, DC CARTER, CS MCARDLE, RJ MILLS Physiotherapy is used routinely to improve postoperative pulmonary dysfunction, but its value is unknown (*Br Med J* 1977;2:1500). Controlled studies were undertaken to assess the effect of (1) physiotherapy on  $\text{PaO}_2$  and (2) routine physiotherapy on the incidence of pulmonary complications. Arterial blood gas analysis was performed before physiotherapy, 30 minutes, and 120 minutes after physiotherapy in 53 patients. Mean  $\text{PaO}_2$  rose from  $68 \pm 1$  mmHg before physiotherapy to  $72 \pm 1$  mmHg 30 minutes after physiotherapy ( $p < 0.001$ ) and to  $71 \pm 1$  mmHg 120 minutes after physiotherapy ( $p < 0.001$ ). After cholecystectomy 102 patients were randomly allocated to receive routine physiotherapy or no physiotherapy. Postoperatively the patients were classified into one of three clinical groups—no complications, atelectasis, or chest infection. Before surgery and for the first four days after operation  $\text{PaO}_2$  was measured. Forty-seven patients had no complications, atelectasis occurred in 29 and chest infection in 26. The pattern of arterial oxygen tensions in patients with pulmonary complications was significantly different from those in the uncomplicated group. Chest infection occurred in 19 of 51 control patients compared with seven of 51 patients given physiotherapy ( $p < 0.02$ ). These results suggest that physiotherapy improves arterial oxygenation and reduces the incidence of chest infection after cholecystectomy.

#### Longitudinal study of lung function in coalminers

RG LOVE, BG MILLER Longitudinal loss of lung function in 1677 coalminers from five British collieries has been calculated from the results of serial cross-sectional epidemiological surveys and compared with measured concurrent individual respirable dust exposures and partially estimated previous cumulative exposures. Loss of forced expired volume in one second ( $\text{FEV}_1$ ) over a period of approximately 11 years was found to increase with previous cumulative exposure to dust after allowing for the effects of age, height, smoking, and overall colliery

differences. This relationship was found to hold with concurrent dust exposure only when colliery differences were ignored. These results confirm by direct measurement inferences drawn indirectly from previous cross-sectional studies of the relationship between  $\text{FEV}_1$  and dust exposure (Rogan *et al. Br J Ind Med* 1973;30:217).

#### Emphysema in coalminers

VA RUCKLEY, A SEATON The relationship of dust inhalation to the development of emphysema remains controversial. We have examined the lungs of 450 coalminers who had in life taken part in an epidemiological study of their respiratory health. They included 45 non-smokers, 60 who had never attended a Pneumoconiosis Panel in their life, and 100 with minimal pathological pneumoconiosis. Emphysema measurements (Heard and Izukawa, *J Path Bact* 1964; 88: 423) showed that the prevalence of both centriacinar and panacinar types related to smoking habit, age at death, and the extent of pneumoconiosis. Centriacinar emphysema in addition was more prevalent the more dust the lungs contained, though centriacinar disease was less likely to occur if the dust contained a high proportion of silica and silicates. Using data obtained in life, we have shown a relationship between evidence of airways obstruction ( $\text{FEV}_1$ ) and the extent of emphysema. The measured dust exposures of the coalminers have been used to examine the possibility that emphysema causes accumulation of dust in the lungs rather than vice versa.

#### Role of atopy in determining susceptibility of smokers to chronic airway narrowing

SJ CONNELLAN, R CARSON, F HOLLAND, H JOYCE, NB PRIDE The factors which predispose a minority of smokers to develop severe chronic airflow obstruction are largely unknown. We have reinvestigated the "Dutch hypothesis" that such smokers have evidence of atopy. In 1980 we re-studied 141 of an original cohort of 277 men born between 1916 and 1931 who had had regular spirometric measurements since 1961 (Fletcher *et al. The natural history of chronic bronchitis and emphysema*. Oxford; Oxford University Press, 1976). Fifteen of these men who showed a decline in  $\text{FEV}_1$  of at least 25% of their initial value or one litre over 20 years, were selected for further study. Each man was matched with a man of similar age, height, and smoking history from the same working population. The mean decline in  $\text{FEV}_1$  for the decliners (D) and controls (C) were  $54.3 \pm 12$  ml  $\text{yr}^{-1}$  and  $33.6 \pm 12$  ml  $\text{yr}^{-1}$  respectively ( $p < 0.001$ ).  $\text{FEV}_1/\text{VC}\%$  in 1980 was  $56.8 \pm 11.6\%$  in group D and  $70.5 \pm 7.3\%$  in group C. Bronchial reactivity to inhaled histamine was assessed by determining the histamine concentration required to cause a fall of 20% in baseline  $\text{FEV}_1$  ( $\text{PC}_{20}$ ); the mean log concentration was  $0.88 \pm 1.46$  mg  $\text{ml}^{-1}$  in group D and  $2.16 \pm 0.91$  mg  $\text{ml}^{-1}$  in group C ( $p = 0.007$ ). Mean scores for prick skin tests to four common allergens were 3.0 in D and 1.2 in C ( $p = 0.03$ ). Differences in total serum IgE were not significant; mean log IgE was  $4.29 \pm 1.78$  units  $\text{ml}^{-1}$  in group D and  $3.55 \pm 1.67$  units  $\text{ml}^{-1}$  in C. Six men of group D and one of group C had first degree relatives with asthma, hayfever, or infantile eczema. Four in group D and none in group C had a personal history of hayfever

or urticaria. These results provide some evidence in support of the Dutch hypothesis but require to be extended to a larger number of subjects.

#### Effect of low frequency fatigue of the sternomastoid muscle on ventilatory performance

SH CARSWELL, NT COOKE, SG SPIRO Low frequency fatigue (LFF) is a possible factor in the development of respiratory failure (Moxham *et al. Thorax* 1980; 35: 226). Two tests—sustained maximum voluntary ventilation (SMVV) for 10 minutes and a 12-minute walk (12MW)—were performed to ascertain whether LFF develops after prolonged ventilatory stress and if subsequent ventilatory performance is affected. Four normal subjects and four patients with chronic obstructive bronchitis ( $FEV_1 1.0 \pm 0.3$  l) were studied. A minute ventilation of 80% maximum breathing capacity (MBC) was reached during SMVV, and LFF developed in all subjects. The four patients showed LFF after the 12 MW, during which their minute ventilation also reached 80% MBC. There was no LFF after the 12 MW in the normal subjects, whose ventilation was 45% of MBC. In the presence of LFF all subjects were able to repeat the fatiguing stress test. Low frequency fatigue develops in normal subjects and patients with chronic obstructive bronchitis at the same relative sustained stress of 80% MBC. We have also demonstrated LFF in patients in acute respiratory failure. In ambulant bronchitic patients LFF may occur during everyday activities without obvious disadvantage but its implications may be more important during an acute respiratory illness.

#### Renal glomerular size in hypoxic cor pulmonale

PMA CALVERLEY, J CAMPBELL, D LAMB, DC FLENLEY The glomeruli of patients with cor pulmonale have been noted to be larger than normal but this remains unexplained. We measured the mean capillary tuft by a custom-built semi-automatic technique in postmortem sections from the kidneys of 16 patients with "blue and bloated" chronic bronchitis and emphysema, and in seven patients of similar age who were free of respiratory or renal disease at death. The patients' mean arterial  $PO_2$  was  $6.9$  SD  $1.2$  kPa, mean arterial  $PCO_2$   $7.2$  SD  $1.2$  kPa, mean red cell mass  $35.3$  SD  $5.4$  ml/kg, and mean pulmonary artery pressure  $28.5$  SD  $5.8$  mm/Hg. Nine bronchitic patients had received domiciliary oxygen therapy while seven had not. The mean tuft area in these treated bronchitics ( $142$  SD  $13$ ,  $10^2 \mu m^2$ ) was not significantly different from the untreated patients ( $168$  SD  $16$ ,  $10^2 \mu m^2$ ) but glomerular tuft area in the bronchitic subjects was significantly larger than that of the non-bronchitic controls ( $121$  SD  $5$ ,  $10^2 \mu m^2$ ,  $p < 0.02$ ). There was no reduction in glomerular cellularity to suggest passive venous distension, and glomerular size was not correlated with clinical or pathological indices of cor pulmonale (including red cell mass). However arterial  $PO_2$  was correlated with glomerular size ( $r = 0.69$ ,  $p < 0.01$ ) if allowance was made for the higher  $PO_2$  of the patients receiving oxygen. The percentage of glomeruli with an identifiable juxtaglomerular apparatus also increased with increasing glomerular size. These structural changes in the kidneys of patients with severe chronic bronchitis and emphysema may reflect changes in

renal salt and water handling which are potentially reversible by oxygen therapy.

#### Ciliary abnormalities on both sides of the Tasman Sea

RH STEELE, STJ WAKEFIELD, CJ BISHOP Bronchiectasis among Polynesians is common and severe. Most cases have shown ciliary and sperm tail ultrastructural abnormalities similar to those in Kartagener's syndrome. However, situs inversus is not present (Waite *et al. Lancet* 1978; 2: 132; Wakefield *Am Rev Respir Dis* 1980; 121: 1003). In Australia since 1978 we have examined 60 patients with either bronchiectasis, chronic sinusitis, chronic otitis media, situs inversus, or combinations of these. These include six cases of Kartagener's syndrome, of whom one has a radial spoke defect (Sturgess *et al. N Engl J Med* 1979; 300: 53) and one may be heterozygous or show incomplete expression of the genetic abnormality. Three cases of immotile cilia syndrome without situs inversus have been found, two of which are aborigines. Like Polynesians, Australian aborigines are very prone to chronic chest infection and it is possible that they also have an increased incidence of an abnormal gene. A variety of abnormalities considered to be acquired has been seen, but in some cases it is impossible to distinguish between severe acquired changes and partial expression of a genetic defect.

#### Leucocyte elastase and serum protease inhibitors in sputum sol phase: effect of steroids

J WIGGINS, JA ELLIOTT, RD STEVENSON, RA STOCKLEY An imbalance between proteases and their inhibitors has been implicated in the pathogenesis of emphysema. It is therefore important to study factors which can influence this balance. We studied the effect of oral prednisone on protease inhibitors and leucocyte elastase in the sol phase sputum of nine patients with obstructive bronchitis. Daily serum and sputum samples were collected for five days while the patient was on placebo and for the last five days of one week's treatment with prednisone 30 mg daily. The sputum to serum ratios of albumin (used as a standard: Stockley *et al. Thorax* 1979; 34: 777) varied from patient to patient, but average values were similar to those found previously  $-0.5 \times 10^{-3}$  (SD  $\pm 0.31 \times 10^{-3}$ ). After treatment with steroids, the ratios fell to  $0.35 \times 10^{-3}$  (SD  $\pm 0.22 \times 10^{-3}$ ) ( $2p < 0.01$ ). A similar fall in sputum to serum  $\alpha_1AT$  ratio was noted, whereas the ratios for  $\alpha_1$  antichymotrypsin rose ( $2p < 0.05$ ) suggesting an increase in local production. Leucocyte elastase concentrations did not alter on treatment from the average control value of  $25.5 \mu g/ml$  (SD  $\pm 15.8$ ). However, it was present in a 5.3 to 1 molar excess compared to  $\alpha_1AT$ . During treatment, this molar excess was greater (7.5 to 1) because of the tendency for sputum  $\alpha_1$  antitrypsin to fall. These results suggest that steroids may adversely affect the protease/inhibitor balance within the lung of patients with obstructive bronchitis.

#### Enhancement of human alveolar macrophage function by lymphokines

AP GREENING, ADM REES, DB LOWRIE Macrophage function can be modified by lymphokines. We examined the

influence of lymphokines on human alveolar macrophage (HAM) hydrogen peroxide ( $H_2O_2$ ) release and bactericidal function. HAM were obtained from patients undergoing diagnostic bronchoscopy. Lymphokines were prepared from human peripheral blood mononuclear cells cultured for five days in the presence of heat-killed *Staphylococcus aureus* or phytohaemagglutinin (PHA). HAM from six patients were incubated with or without lymphokine for three days, *in vitro*. Six staphylococcus-induced and three PHA-induced lymphokine preparations, in concentrations from 1 to 50%, all primed HAM for enhanced  $H_2O_2$  release in response to stimulation with phorbol myristate acetate (130–360%  $H_2O_2$  relative to control HAM); this effect varied with both the batch and the concentration of lymphokine preparation. Treatment of another six HAM preparations with three lymphokines improved intracellular staphylococcal killing (methods as per Greening and Lowrie, *Clin Sci* 1980;59:14P) by the HAM as compared with controls (mean 30% fewer live bacteria at four hours). We conclude that lymphokines can enhance the microbicidal function of HAM. This may be related to their ability to prime HAM for enhanced  $H_2O_2$  release. The enhanced peroxide response may also be relevant to the lung tissue damage observed in diseases with prominent cell-mediated immunity.

#### Mast cells in the human alveolar wall

B FOX, TB BULL, A GUZ Mast cells were identified by electronmicroscopy in the alveolar wall of human lungs in 20 surgically removed specimens. In 10 the pieces of lung examined by routine histological examination were normal and in 10 abnormal. A quantitative and qualitative study was made of the mast cells. There was an average of 350 mast cells/mm<sup>2</sup> of alveolar wall in the normal and 523/mm<sup>2</sup> in the abnormal specimens: the difference was not statistically significant. Mast cells occupied from 1.6–2.1% of the area of the alveolar wall.

There was marked variation in the structure of the mast cell granules but no difference between those in the normal and abnormal lung. The appearance of the mast cell granules suggest that constant degranulation may be occurring within the lung. The role that alveolar mast cells may play in the vasoconstrictor response to alveolar hypoxia will be discussed. It will be suggested that the characteristic tachypnoea of allergic asthma may in part be caused by the release of mediators from sensitised mast cells within the alveolar wall.

#### Low frequency breath sounds in respiratory disease

SW BANHAM, RB URQUHART, JES MACLEOD, F MORAN Considerable interest in pulmonary sounds has developed as a result of the work of Forgacs (Forgacs, *Lung sounds*. London: Baillière Tindal, 1978) which provided a rational basis for these sounds in terms of the physiological and pathological processes within the respiratory system. Crackling has received particular attention and analysis of electronic recordings by techniques such as the time-expanded wave form (Murphy *et al. N Engl J Med* 1977; 296:969) have enabled some differentiation between the conditions associated with pulmonary crackles. We have recorded the pulmonary sounds in five normal adult males, five patients with asbestosis and crackling, and five patients with pulmonary oedema. The details of the methods and computer-based analysis employed are reported elsewhere (Urquhart *et al. Comput Biol Med* 1981; in press), but the technique used enabled very low frequency spectra, inaudible to the human ear, to be extracted without any contribution from the crackling. These low frequencies (0–50 Hz) were compared using 70 spectra from each group and the data were correctly separated into the three categories on this basis alone. Alteration in low frequency breath sounds may provide useful additional information to the adventitious sounds in the diagnosis of respiratory disorders.